Diabetic Control And Cardiac Survival In CKD And Dialysis Patient

By

Mohamed Sobh MD,FACP

Prof.of Nephrology-Urology&Nephrology Center-Mansoura Faculty of Medicine

Introduction

- Diabetic dialysis patients are at very high risk for vascular complications .More than 23% of incident diabetic dialysis patients in US will succumb to cardiovascular and infectious complications during their first year of renal replacement therapy and only 31% survive 5 years (1)

- Survival in patient on hemodialysis is related to glycemic control (2,3)

- Moreover, even mild degree of hyperglycemia in nondiabetic dialysis population have been associated with reduce survival (4)

(1) US Renal Data system .USRD 2006 Annual Data report .Atlas of end-stage renal disease in the US, NIH , National institute of diabetes and digestive and kidney : Bethesda ,MD,2006

(2) Oomichi T et al .Diabetes 2006 ;29:1496-1500

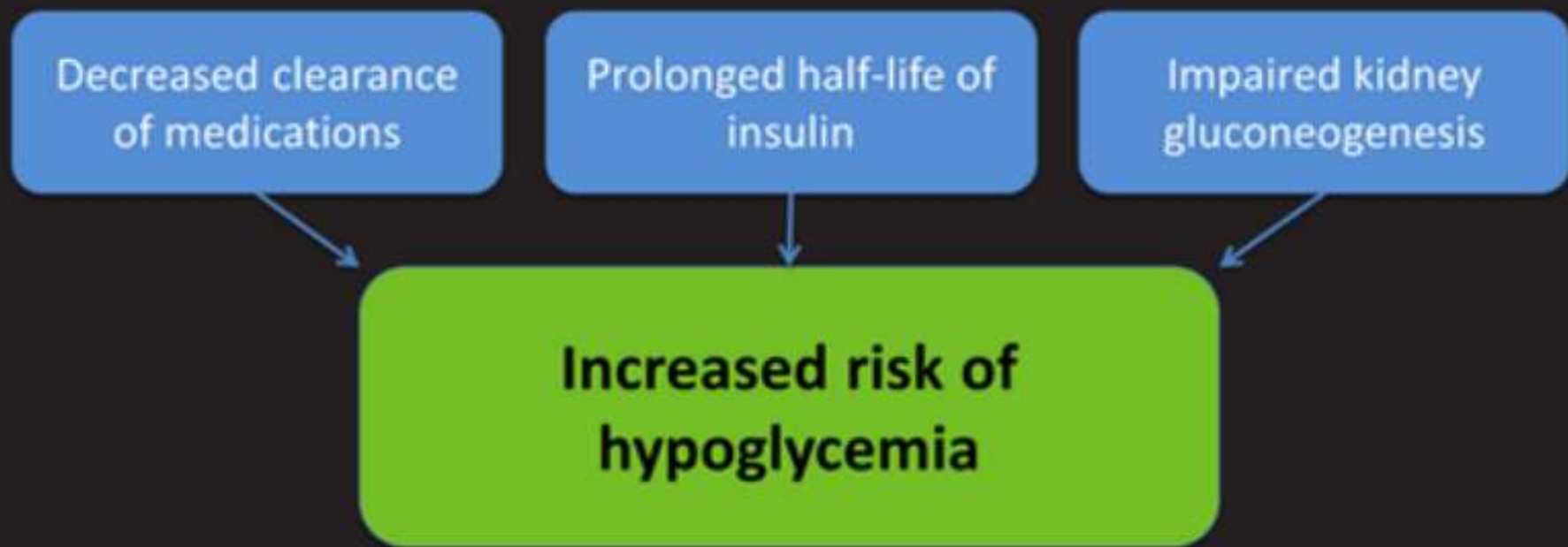(3) Kalantar-Zadeh K et al Diabetes care 2007 ; 30 :1049-1055

(4) lin-Tan DT et al. Jam soc Nephro 2007 :18:2385-2391

Goals of the antidiabetic Treatment

- Optimal and persistent Blood Glucose lowering (HbA1c< 7.0 % or <6.5%)
- Prevention of progression of ß-cell Failure
- Lower rate of side effects of the antidiabetic Drugs:
   Hypoglycemia , Gastrointestinal side Effects,
   weight gain ,Edema , Heart failure, Bone Fractures.
- Primary prevention of vascular complications .
- Secondary prevention of vascular complications.

Selecting Appropriate Antihyperglycemics in CKD

Decreased clearance of medications	Prolonged half-life of insulin	Impaired kidney gluconeogenesis

Increased risk of hypoglycemia

- Necessitates greater care with monitoring and selection of agents

Antihyperglycemic Agents

- Sulfonylureas (glyburide, glimepiride, glipizide, others)
- Meglitinides (nateglinide and repaglinide)
- Biguanides (metformin)
- Bile sequestrants (colesevelam)
- Ergoline (quick-release bromocriptine)
- Alpha-glucosidase inhibitors (acarbose and miglitol)
- Thiazolidinediones (pioglitazone and rosiglitazone)
- Incretins
  - GLP-1 receptor agonists (immediate-release exenatide, extended-release exenatide, liraglutide)
  - DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin)
- Insulin

Non-insulin antihyperglycemic agents

AGENTS	MECHANISM	INITIAL DOSE	MAXIMUM DOSE	ADVERSE EFFECTS	USE IN RENAL FAILURE
Sulfonylureas	Increase insulin secretion by pancreatic beta cells			Hypoglycemia and weight gain	Metabolism is affected by renal failure, necessitating dosage reduction and eventually avoidance
Glyburide (Micronase)		2.5–5 mg/day	10 mg twice daily		Used at doses of 2.5–5 mg/day if GFR > 50 mL/minute Not safe
Glimeperide (Amaryl)		1 mg/day	8 mg/day		Not safe
Glipizide (Glucotrol)		5 mg/day or XL 5 mg/day	20 mg twice daily or XL 20 mg/day		Safe at dosage of 2.5–10 mg/day Extended-release form is not safe
Tolbutamide (Orinase)		500 mg twice daily	500 mg four times a day		Not used
Chlorpropamide (Diabinese)		100 mg/day	500 mg/day		Not used
Meglitinides	Increase insulin secretion by pancreatic beta cells			Hypoglycemia and weight gain	Can be used
Repaglinide (Prandin)		0.5 mg three times a day	4 mg three times a day		May be used with caution, but is best avoided
Nateglinide (Starlix)		120 mg three times a day	180 mg three times a day		Hepatically metabolized and active metabolites excreted by kidneys; hence, not safe

Class / Drug	Mechanism	Starting dose	Maximum dose	Adverse effects	Renal considerations
Biguanides	Decrease hepatic gluconeogenesis			No hypoglycemia or weight gain	Contraindicated when GFR is < 60 mL/minute
Metformin (Glucophage)		250 mg twice daily	850 mg three times daily		
Thiazolidinediones	PPAR-gamma agonists; lower insulin resistance and enhance peripheral disposal of glucose			Cause weight gain; no hypoglycemia	Metabolism not affected; caution in patients with congestive heart failure
Rosiglitazone (Avandia)		4 mg/day	8 mg/day		
Pioglitazone (Actos)		15 mg/day	45 mg/day		
Alpha-glucosidase inhibitors	Prevent digestion of carbohydrates			No hypoglycemia or weight gain	Contraindicated because of increased level of parent drug and metabolite
Acarbose (Precose)		25 mg three times daily	100 mg three times daily		
Miglitol (Glyset)		25 mg three times daily	100 mg three times daily		
GLP-1 analogues	Slow gastric emptying, increase postprandial insulin release, reduce glucagon release				
Exenatide (Byetta)		5–10 µg twice daily	10 µg twice daily	Nausea, vomiting, and weight loss	Contraindicated if GFR is < 30 mL/min, and in ESRD
'Gliptins'	Inhibit DPP-IV, enhance action of GLP-1			Gastrointestinal effects; risk of hypoglycemia if used with sulfonylureas	
Sitagliptin (Januvia)		25 mg/day	100 mg/day		50 mg/day if GFR is 30–50 mL/min, or 25 mg/day if GFR < 30 or in ESRD
Saxagliptin (Onglyza)		2.5 mg/day	5 mg/day	Headache, upper respiratory infection, urinary tract infection	2.5 mg/day if GFR < 50 mL/min and in hemodialysis patients; not studied in peritoneal dialysis

GFR = glomerular filtration rate; ESRD = end-stage renal disease; DPP-IV = dipeptidyl peptidase; GLP-1 = glucagon-like peptide-1; PPAR-gamma = peroxisome proliferator-activated receptor gamma
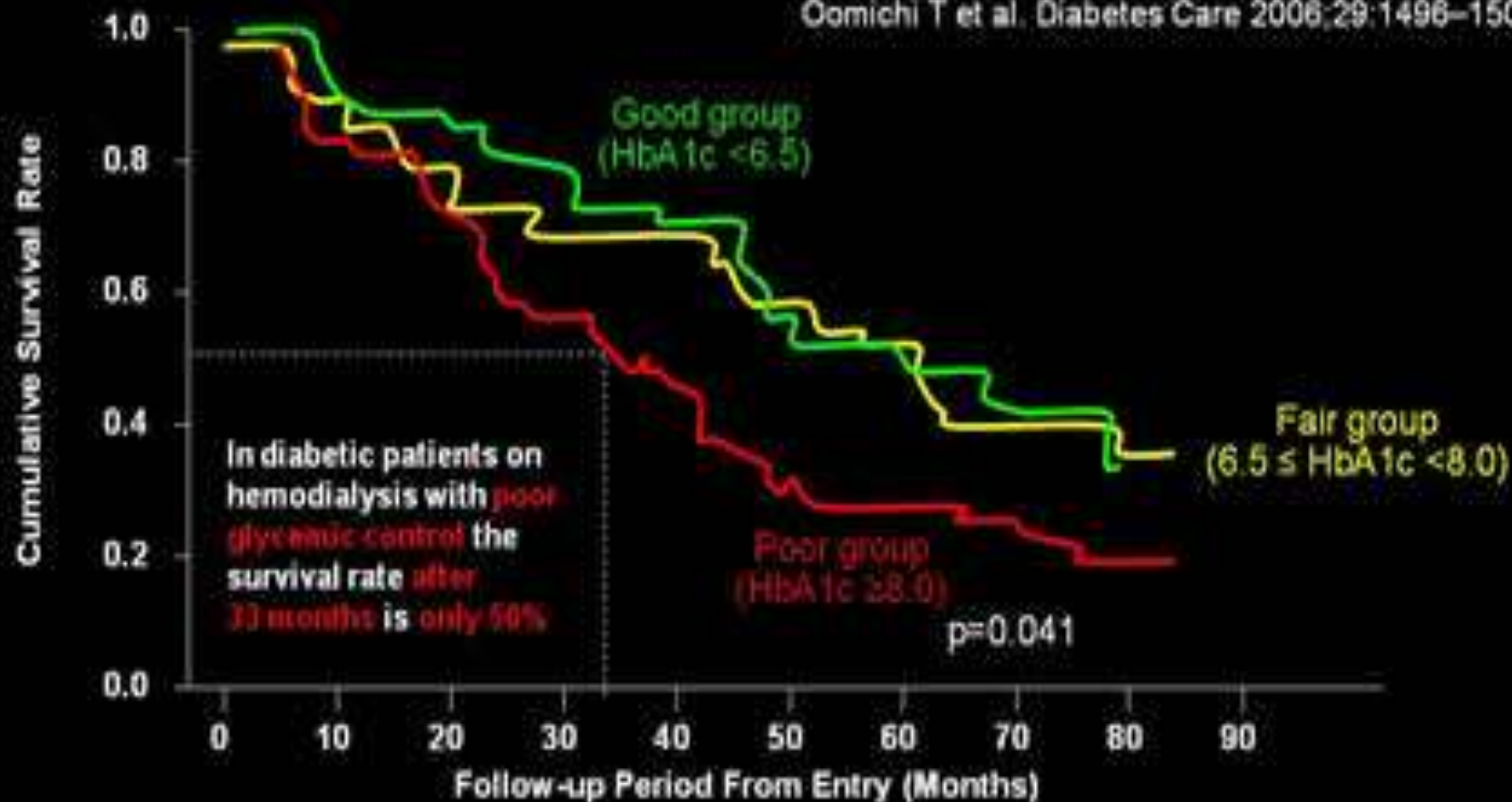
Insulin preparations: Considerations in hemodialysis patients

INSULIN PREPARATION	ONSET OF ACTION	PEAK ACTION	EFFECTIVE DURATION	DOSING CHANGE IN RENAL FAILURE
Rapid-acting				Reduce dose by 25% when glomerular filtration rate (GFR) is 10–50 mL/min, and by 50% when GFR < 10 mL/min
Regular	30–60 min	2–3 hr	8–10 hr	
Lispro (Humalog)	5–15 min	30–90 min	4–6 hr	
Aspart (NovoLog)	5–15 min	30–90 min	4–6 hr	
Long-acting				Reduce dose by 25% when GFR is 10–50 mL/min, and by 50% when GFR is less than 10 mL/min
Neutral protamine Hagedorn (NPH)	2–4 hr	4–10 hr	12–18 hr	
Glargine (Lantus)	2–4 hr	None	20–24 hr	
Detemir (Levemir)	3–4 hr	3–14 hr	6–23 (19.9) hr	
Premixed				Reduce dose by 25% when GFR is 10–50 mL/min, and by 50% when GFR is less than 10 mL/min
70/30 human mix	30–60 min	3–12 hr	12–18 hr	
70/30 aspart mix	5–15 min	30–90 min	12–18 hr	
75/25 lispro mix	5–15 min	30–90 min	12–18 hr	

Impact of Glycemic Control on Survival of Diabetic Patients on Chronic Regular Hemodialysis: A 7-year Observational Study

Oomichi T et al. Diabetes Care 2006;29:1496–1500

Good group (HbA1c <6.5)

Fair group (6.5 ≤ HbA1c <8.0)

Poor group (HbA1c ≥8.0)

In diabetic patients on hemodialysis with poor glycemic control the survival rate after 33 months is only 50%

p=0.041

Cumulative Survival Rate

Follow-up Period From Entry (Months)

This finding indicates that careful glycemic control after initiation of hemodialysis is very important

HbA1c and survival Maintenance Hemodialysis Patients

- Unadjusted survival analyses in 23,618 diabetic HD patient indicated paradoxically lower death hazard ratios (HRs) with higher A1C values

- However , after adjusting for confounders – malnutrition and anemia – higher HbA1c values were incrementally associated with higher death risks.

- Compared with HbA1c in the 5-6% were 1.41 and 1.73(p<0.001).

- Conclusion:lower HbA1c levels- not related to malnutrition or anemia- appear to be associated with improved survival in diabetic HD patients

- Kalantar-Zadeh et al.Diabetic Care 2007, 30: 1049-1055.

Glycemic Control and Cardiovascular Mortality in Hemodialysis Patients With Diabetes
A 6-Year Cohort Study

Joni Ricks,1 Miklos Z. Molnar,1,2 Csaba P. Kovesdy,3,4 Anuja Shah,5 Allen R. Nissenson,6,Mark Williams,8 and Kamyar Kalantar-Zadeh1,5,7,9

- Previous observational studies using differing methodologies have yielded inconsistent results regarding the association between glycemic control and outcomes in diabetic patients receiving maintenance hemodialysis (MHD). We examined mortality predictability of A1C and random serum glucose over time in a contemporary cohort of 54,757 diabetic MHD patients (age 63±13 years, 51% men, 30% African Americans, 19% Hispanics). Adjusted all-cause death hazard ratio (HR) for baseline A1C increments of 8.0–8.9, 9.0–9.9, and ≥10%, compared with 7.0– 7.9% (reference), was 1.06 (95% CI 1.01–1.12), 1.05 (0.99–1.12), and 1.19 (1.12–1.28), respectively, and for time-averaged A1C was 1.11 (1.05–1.16), 1.36 (1.27–1.45), and 1.59 (1.46–1.72). A symmetric increase in mortality also occurred with time-averaged A1C levels in the low range (6.0–6.9%, HR 1.05 [95% CI 1.01–1.08]; 5.0– 5.9%, 1.08 [1.04–1.11], and #5%, 1.35 [1.29–1.42]) compared with 7.0–7.9% in fully adjusted models. Adjusted all-cause death HR for time-averaged blood glucose 175–199, 200–249, 250–299, and $300 mg/dL, compared with 150–175 mg/dL (reference), was 1.03 (95% CI 0.99–1.07), 1.14 (1.10–1.19), 1.30 (1.23–1.37), and 1.66 (1.56–1.76), respectively. Hence, poor glycemic control (A1C≥ 8% or serum glucose ≥200 mg/dL) appears to be associated with high all-cause and cardiovascular death in MHD patients. Very low glycemic levels are also associated with high mortality risk.
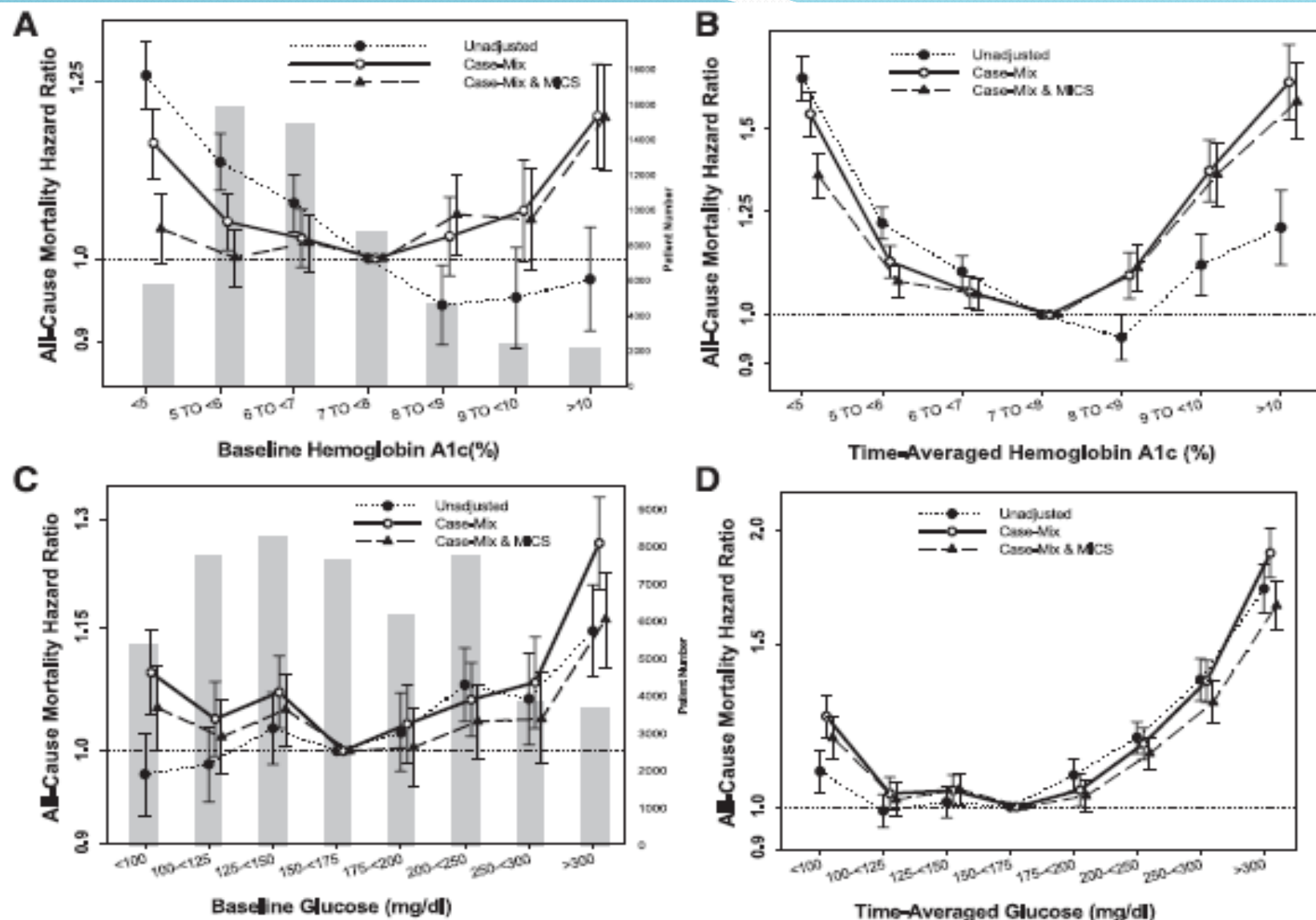
- Diabetes 61:708–715, 2012

FIG. 1. HRs of all cause mortality of the entire range of A1C in 54,757 MHD patients using standard Cox proportional hazards regression (A), a time averaged model (B), and HRs of all cause mortality of serum glucose in 50,383 diabetic MHD patients using standard Cox proportional hazards regression (C) and a time averaged model (D). Case mix model is adjusted for age, sex, race and ethnicity, categories of dialysis vintage, primary insurance, marital status, dialysis dose as indicated by Kt/V (single pool), and residual renal function during the entry quarter. MICS adjusted model includes all of the case mix covariates as well as BMI, nPCR, serum levels of albumin, total iron binding capacity, ferritin, creatinine, phosphorus, calcium, bicarbonate, blood white blood cell count, lymphocyte percentage, and hemoglobin.
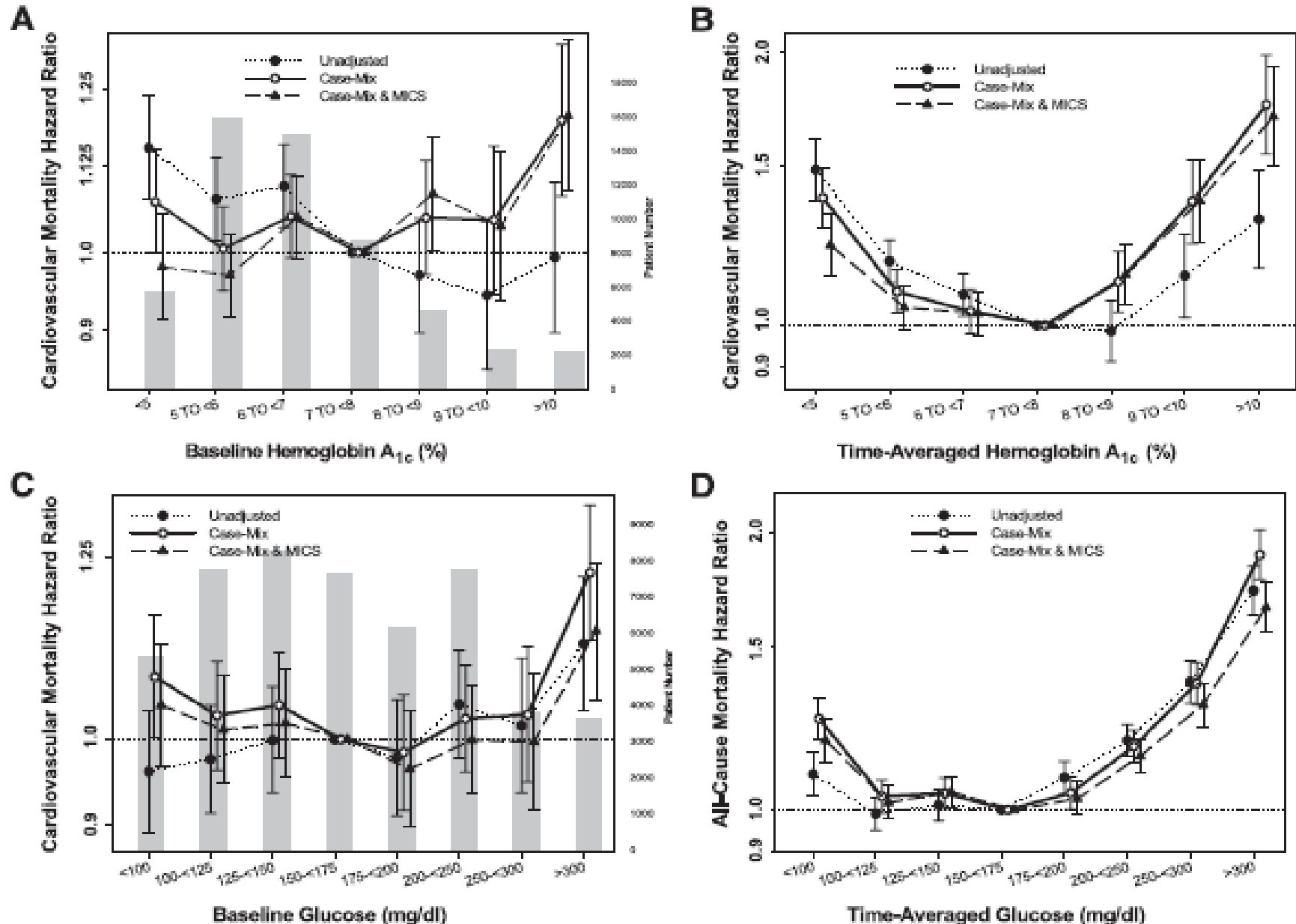
FIG. 3. HRs of cardiovascular mortality of the entire range of A1C in 54,757 MHD patients using standard Cox proportional hazards regression (A), a time averaged model (B), and HRs of cardiovascular mortality of serum glucose in 50,383 diabetic MHD patients using standard Cox proportional hazards regression (C) and a time averaged model (D). Case mix model is adjusted for age, sex, race and ethnicity, categories of dialysis vintage, primary insurance, marital status, dialysis dose as indicated by Kt/V (single pool), and residual renal function during the entry quarter. MICS adjusted model includes all of the case mix covariates as well as BMI, nPCR, serum levels of albumin, total iron binding capacity, ferritin, creatinine, phosphorus, calcium, bicarbonate, blood white blood cell count, lymphocyte percentage, and hemoglobin.

Glycemic Control Is a Predictor of Survival for Diabetic Patients on Hemodialysis

- **OBJECTIVE— To investigate the impact of glycemic control on the survival of diabetic** subjects with end-stage renal disease (ESRD) starting hemodialysis treatment.

- **RESEARCH DESIGN AND METHODS— This single-center prospective observational** study enrolled 150 diabetic ESRD subjects (109 men and 41 women; age at hemodialysis initiation, 60.5 6 10.2 years) at start of hemodialysis between January 1989 and December 1997. The subjects were divided into groups according to their glycemic control level at inclusion as follows: good HbA1c ,7.5%, n 5 93 (group G), and poor HbA1c $7.5%, n 5 57 (group P); and survival was followed until December 1999, with a mean follow-up period of 2.7 years.

- **RESULTS— Group G had better survival than group P (the control group) (P 5 0.008). At** inclusion, there was no significant difference in age, sex, systolic blood pressure (SBP), BMI, cardio-to-thoracic ratio (CTR) on chest X-ray, and serum creatinine (Cre) or hemoglobin (Hb) levels between the two groups. After adjustment for age and sex, HbA1c was a significant predictor of survival (hazard ratio 1.133 per 1.0% increment of HbA1c, 95% CI 1.028 –1.249, P 5 0.012), as were Cre and CTR.

- **CONCLUSIONS— Good glycemic control (HbA1c ,7.5%) predicts better survival of diabetic** ESRD patients starting hemodialysis treatment,

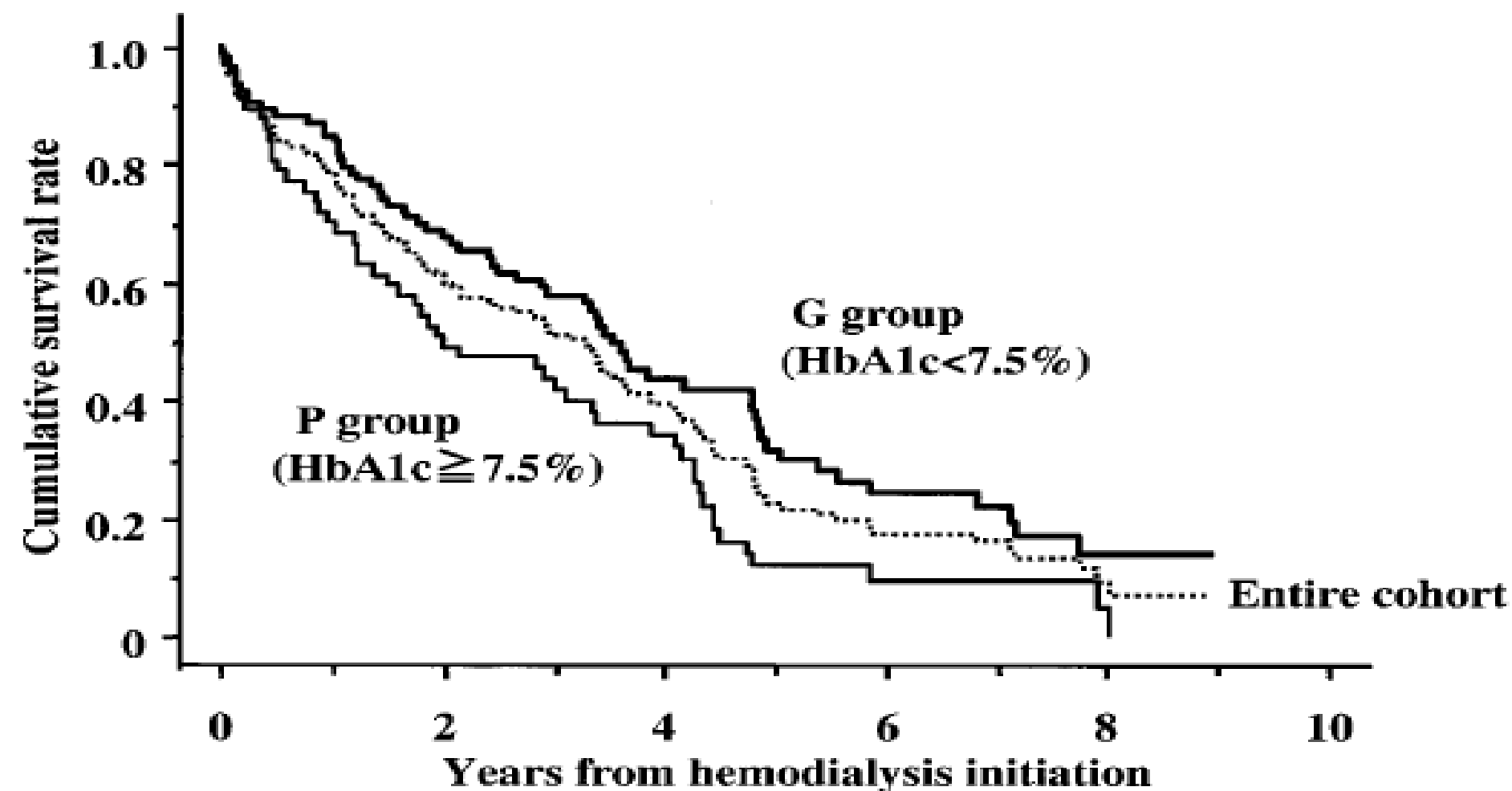**TOMOAKI MORIOKA, MD etal.** *Diabetes Care 24:909–913, 2001*

Figure 1—*Cumulative survival curves for diabetic ESRD subjects on hemodialysis with good (G group) and poor (P group) glycemic control. All diabetic ESRD subjects were divided into two groups by HbA_{1c} level before the initiation of hemodialysis: G group, good glycemic control group ($HbA_{1c} < 7.5\%$), and P group, poor glycemic control ($HbA_{1c} \geq 7.5\%$). The cumulative survival curve for all diabetic ESRD subjects is represented as a dotted line, that of the G group as a thick solid line, and that of the P group as a thin solid line. The cumulative survival curve of the G group was significantly better than that of the P group ($P = 0.005$, log-rank test).*

Table 3—HRs of possible predictive variables for survival of diabetic subjects on hemodialysis (n = 150)

Variables	Unadjusted			Adjusted for age and sex		
	HR	95% CI	P	HR	95% CI	P
Age (year)	1.028	1.009–1.048	0.004*	—	—	—
Sex (female)	0.913	0.604–1.381	0.667	—	—	—
SBP (mmHg)	0.996	0.987–1.005	0.360	0.993	0.984–1.002	0.126
DBP (mmHg)	0.999	0.984–1.013	0.844	1.000	0.986–1.015	0.977
BMI (kg/m^2)	0.950	0.881–1.025	0.186	0.952	0.882–1.027	0.199
CTR (%)	1.033	1.004–1.062	0.025*	1.038	1.003–1.074	0.031*
Cre (mg/dl)	0.920	0.859–0.986	0.018*	0.930	0.867–0.997	0.042*
HbA$_{1c}$ (%)	1.116	1.011–1.232	0.029*	1.133	1.028–1.249	0.012*
Na (mEq/l)	0.981	0.955–1.008	0.162	0.975	0.949–1.001	0.060
K (mEq/l)	0.813	0.642–1.030	0.086	0.840	0.663–1.164	0.148
TP (g/dl)	0.857	0.680–1.080	0.190	0.855	0.675–1.083	0.194
Hb (g/dl)	1.066	0.947–1.199	0.289	1.103	0.973–1.251	0.126
T-chol (mg/dl)	0.997	0.994–1.000	0.040*	0.997	0.994–1.000	0.099

The HR for each variable is expressed per increment of 1 unit of each variable; the HR for sex refers to females. *$P < 0.05$.

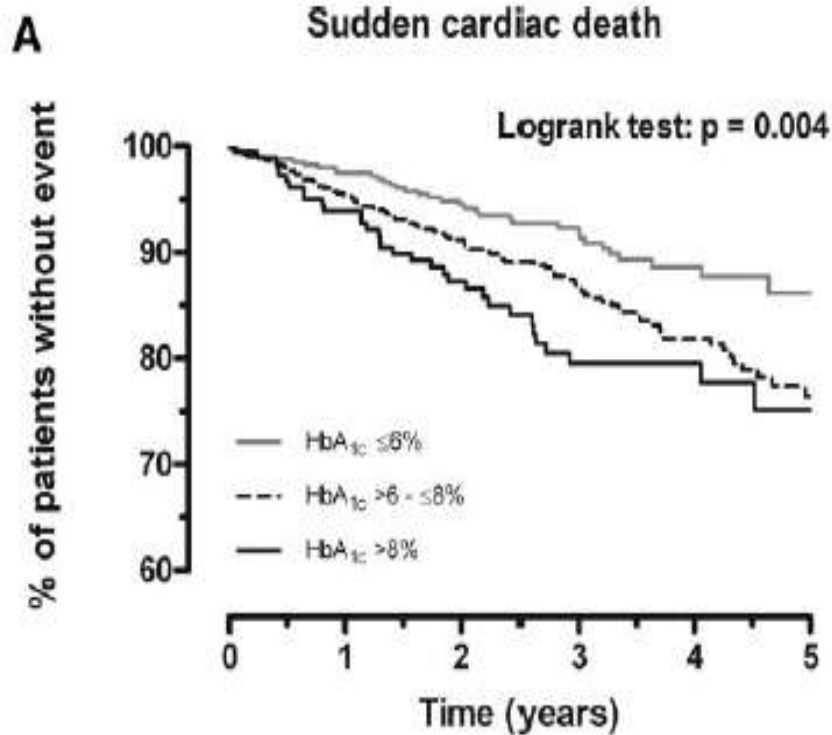Table 4—*Causes of death of diabetic subjects on hemodialysis*

Cause of death	G group	P group	Both groups
Cardiovascular disease	19	12	31
Infectious disease	5	9	14
Pneumonia	3	5	8
Sepsis	2	4	6
Malignant disease	7	2	9
Bleeding	4	3	7
Liver disease	1	1	2
Other	7	2	9
Total	43	29	72

Values are n. The G group consists of subjects with $HbA_{1c} < 7.5\%$, and the P group consists of subjects with $HbA_{1c} \geq 7.5\%$ at hemodialysis initiation.

Glycemic Control and Cardiovascular Events in Diabetic Hemodialysis Patients

Christiane Drechsler, MD, MSc; Vera Krane, MD; Eberhard Ritz, MD; Winfried März, MD; Christoph Wanner, MD

- *Background—Patients on maintenance dialysis treatment experience an excess mortality, predominantly of sudden cardiac* death. Poor glycemic control is associated with cardiovascular comorbidities in the general population,

- This study investigated the impact of glycemic control on cardiac and vascular outcomes in diabetic hemodialysis patients.

- *Methods and Results—Glycohemoglobin A1c (HbA1c) was measured in <u>1255 hemodialysis patients with type 2 diabetes</u> mellitus* who participated in the German Diabetes and Dialysis Study (4D Study) and were <u>followed up for a median of 4 years</u>. Using Cox regression analyses, we determined hazard ratios to reach prespecified, adjudicated end points according to HbA1c levels at baseline: <u>sudden cardiac death (n160), myocardial infarction (n200), stroke (n103), cardiovascular events (n469), death caused by heart failure (n41), and all-cause mortality (n617)</u>. Patients had a mean age of 668 years (54% male) and mean HbA1c of 6.71.3%. Patients with an HbA1c 8% had a 2-fold higher risk of sudden death compared with those with an HbA1c 6% (hazard ratio, 2.14; 95% confidence interval, 1.33 to 3.44), persisting in multivariate models. With each 1% increase in HbA1c, the risk of sudden death rose significantly by 18%; similarly, cardiovascular events and mortality increased by 8%. There was a trend for higher risks of stroke and deaths resulting from heart failure, whereas myocardial infarction was not affected. The increased risks of both cardiovascular events and mortality were explained mainly by the impact of HbA1c on sudden death.

- *Conclusions—Poor glycemic control was strongly associated with sudden cardiac death in diabetic hemodialysis patients,* which accounted for increased cardiovascular events and mortality. In contrast, myocardial infarction was not affected. Whether interventions achieving tight glycemic control decrease sudden death requires further evaluation.
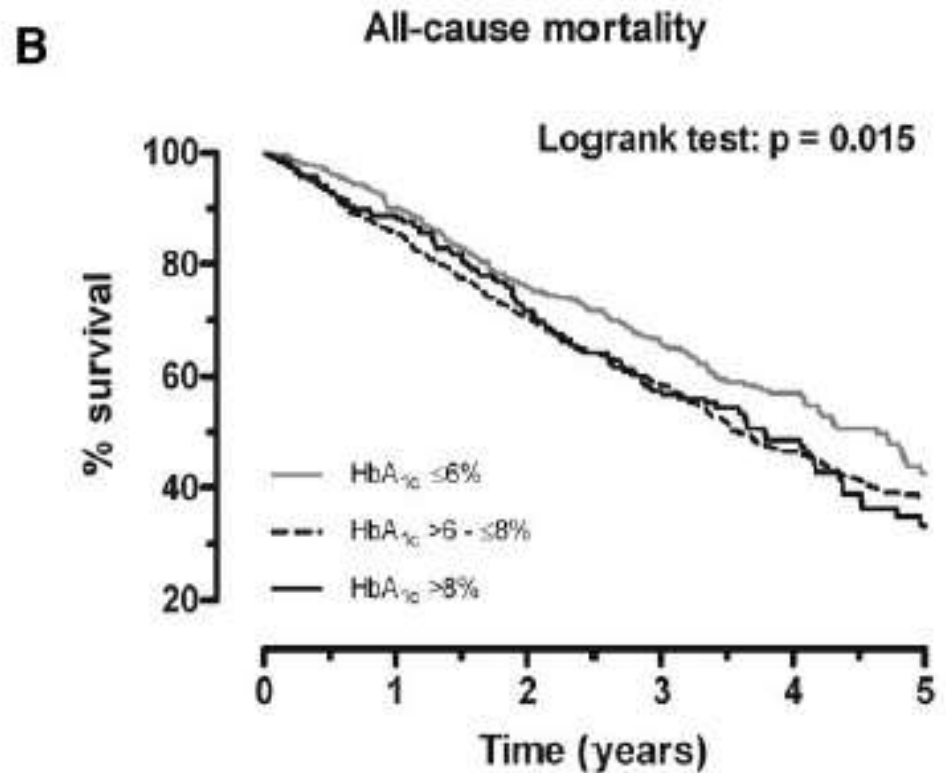
Figure. Kaplan–Meier curves for the time to sudden cardiac death (A) and all-cause mortality (B) in subgroups of patients according to baseline HbA1c levels (HbA1c 6% [reference group]; HbA1c 6% to 8%; HbA1c 8%).

Poor Glycemic Control is a Significant Predictor of Cardiovascular Events in Chronic Hemodialysis Patients With Diabetes

- **Abstract: We investigated the impact of glycemic control** on the emergence of cardiovascular disease (CVD) in diabetic patients who were on maintenance hemodialysis in a prospective observational study. One hundred and thirtyfour diabetic hemodialysis patients (63 ± 10 years-old, hemodialysis duration of 4.5 ± 3.9 years) at a single dialysis center were enrolled. The cohort was observed prospectively for 5 years, and the emergence of fatal and non-fatal CVD was recorded. Patients were categorized into two groups; good (mean hemoglobin (Hb) A1C <7.0%, N = 65) and poor HbA1C (mean HbA1C 7.0%,N = 69).*The relationship* between glycemic control and CVD emergence was evaluated by Kaplan-Meier estimation and Cox proportional hazard models. During the follow-up period, 50 CVD events were observed. The cumulative CVD incidence in the poor HbA1C group was significantly higher than that of the good HbA1C group, as determined by Kaplan-Meier estimation (*P = 0.0250, log-rank test*). *After* adjustment for gender, age, duration of dialysis, and past history of CVD, a multivariate Cox proportional hazard model showed that poor HbA1C was a significant predictor of CVD events (hazards ratio [HR] 1.828 [95% CI, 1.008– 3.314], *P = 0.0470*). *When ischemic heart disease, cerebral* infarction, and arteriosclerosis obliterans were determined as an endpoint, both HbA1C levels and the poor HbA1C group were significant predictors for the emergence of CVD (HR 1.269 per 1% HbA1C [95%CI, 1.022–1.574], *P = 0.0307,and HR 2.816 [95% CI, 1.377–5.759],P = 0.0046*, respectively).

- In diabetic hemodialysis patients, poor glycemic control is a significant, independent predictor of the emergence of CVD, indicating the importance of careful management of glycemic control in hemodialysis patients.

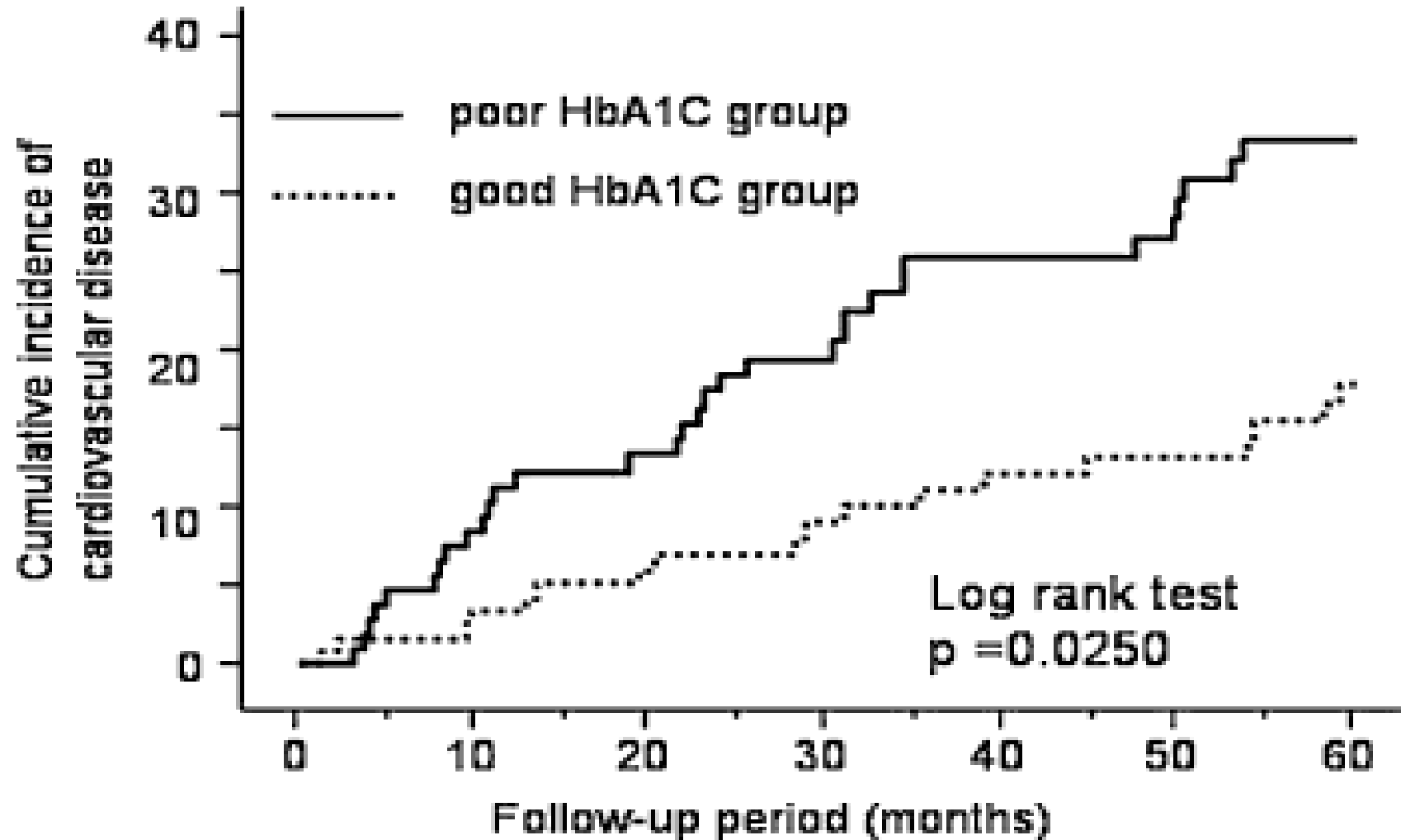- Yoshihiro Tsujimoto,et al . *Ther Apher Dial, Vol. 13, No. 4, 2009*

FIG. 1. Kaplan-Meier estimation of cumulative incidence of cardiovascular diseases during the 5-year, prospective, follow-up study. The poor hemoglobin (Hb) A1C group (HbA1C $\geq 7.0\%$) showed a significantly higher incidence of new emergence of cardiovascular diseases than the good HbA1C group (HbA1C $<7.0\%$) ($P < 0.05$, log-rank test).

TABLE 2. *Number of patients with cardiovascular events during the observational periods, according to glycemic control*

		Good HbA1C group	Poor HbA1C group
		($N = 65$)	($N = 69$)
Ischemic heart disease	total	3	11*
	(fatal/nonfatal)	1/2	3/8
Cerebral infarction	total	5	12
	(fatal/nonfatal)	(0/5)	(0/12)
Cerebral hemorrhage	total	7	3
	(fatal/nonfatal)	(2/5)	(1/2)
Arteriosclerosis obliterans	total	3	6
	(fatal/nonfatal)	(1/2)	(4/2)
Total (%)		18 (27.7%)	32* (46.4%)

Hb, hemoglobin.

*$P < 0.05$ vs. good HbA1C group. (x^2 test). Good HbA1C group, HbA1C <7.0%; Poor HbA1C group, HbA1C ≥7.0%.

TABLE 3. *Univariate Cox proportional hazards model for the emergence of cardiovascular disease*

	HR	95%CI	P-value
Gender (male = 1)	0.893	0.492–1.618	0.7085
Age (years)	0.994	0.967–1.022	0.6856
Duration of dialysis (years)	1.017	0.950–1.088	0.6242
BMI (kg m^2)	0.994	0.908–1.088	0.8971
Systolic blood pressure (mm Hg)	1.008	0.989–1.028	0.3899
Diastolic blood pressure (mm Hg)	1.017	0.979–1.056	0.3902
Creatinine (mg/dL)	0.929	0.834–1.033	0.1745
Albumin (g/dL)	0.595	0.232–1.524	0.2788
Total cholesterol (mg/dL)	1.003	0.996–1.010	0.3598
C-reactive protein (mg/dL)	0.880	0.631–1.225	0.4481
Hemoglobin (g/dL)	0.973	0.773–1.224	0.8127
Past history of CVD (yes/no)	1.562	0.860–2.837	0.1428
HbA1C (%)	1.179	0.976–1.422	0.0870
HbA1C group (poor vs. good)	1.916	1.074–3.417	0.0277

BMI, body mass index; CVD, cardiovascular disease; HR, hazards ratio.

TABLE 4. *Multivariate Cox proportional hazards model for the emergence of cardiovascular diseases*

	Model 1			Model 2		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender (male = 1)	0.924	0.498–1.717	0.8031	0.955	0.516–1.768	0.8842
Age (years)	0.995	0.967–1.023	0.7302	0.997	0.969–1.026	0.8543
Duration of dialysis (years)	1.013	0.943–1.089	0.7159	1.012	0.942–1.088	0.7413
Past history of CVD (yes = 1)	1.473	0.792–2.740	0.2209	1.459	0.786–2.710	0.2314
HbA1C (%)	1.156	0.950–1.408	0.1477	–	–	–
HbA1C group (poor vs. good)	–	–	–	1.828	1.008–3.314	0.0470

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio.

TABLE 5. *Multivariate Cox proportional hazards model for arterio-occlusive cardiovascular diseases*

	Model 1			Model 2		
	HR	95%CI	P-value	HR	95%CI	P-value
Gender (male = 1)	0.980	0.491–1.956	0.9550	1.025	0.517–2.030	0.9439
Age (years)	0.997	0.967–1.028	0.8545	1.001	0.970–1.033	0.9601
Duration of dialysis (year)	1.019	0.940–1.104	0.6478	1.018	0.938–1.104	0.6749
Past history of CVD (yes = 1)	1.233	0.592–2.568	0.5764	1.182	0.569–2.453	0.6542
HbA1C (%)	1.269	1.022–1.574	0.0307	–	–	–
HbA1C group (poor vs. good)	–	–	–	2.816	1.377–5.759	0.0046

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio.
Arterio-occlusive cardiovascular diseases include ischemic heart disease, cerebral infarction, and arteriosclerosis obliterans.

Association of HbA1c Values with Mortality and Cardiovascular Events in Diabetic Dialysis Patients. The INVOR Study and Review of the Literature

- Abstract
- Background: Improved glycemic control reduces complications in patients with diabetes mellitus (DM). However, it is discussed controversially whether patients with diabetes mellitus and end-stage renal disease benefit from strict glycemic control.
- Methods: We followed <u>78 patients with DM initiating dialysis treatment</u> of the region of Vorarlberg in a prospective cohort study applying a time-dependent Cox regression analysis using all measured laboratory values <u>for up to more than seven years</u>. This resulted in 880 HbA1c measurements (with one measurement every 3.16 patient months on average) during the entire observation period. Non-linear P-splines were used to allow flexible modeling of the association with mortality and cardiovascular disease (CVD) events.
- Results: We observed a decreased mortality risk with increasing HbA1c values (HR = 0.72 per 1% increase, p = 0.024).

  Adjustment for age and sex and additional adjustment for other CVD risk factors only slightly attenuated the association (HR = 0.71, p = 0.044). A non-linear P-spline showed that the association did not follow a fully linear pattern with a highly significant non-linear component (p = 0.001) with an increased risk of all-cause mortality for HbA1c values up to 6–7%. Causes of death were associated with HbA1c values. The risk for CVD events, however, increased with increasing HbA1 values (HR = 1.24 per 1% increase, p = 0.048) but vanished after extended adjustments.
- Conclusions: This study considered the entire information collected on HbA1c over a period of more than seven years. Besides the methodological advantages <u>our data indicate a significant inverse association between HbA1c levels and allcause mortality. However, for CVD events no significant association could be found.</u>

Metabolic control and vascular diseases under oral antidiabetic drug versus insulin therapy and/or diet alone during the first year of hemodialysis in type 2 diabetic patients with ESRD

Abstract

- Introduction Uremic type 2 diabetic patients on hemodialysis need various types of antidiabetic therapies.

- The aim of the present study was to identify differences between patients on oral antidiabetic drug therapy or insulin substitution or diet therapy alone during their first year of hemodialysis.

- Patients and methods <u>Sixty-four type 2 diabetic patients</u> who had started hemodialysis (HD) at our dialysis center <u>between 2003 and 2007</u> were included in the study. Kidney-transplanted patients (n = 1) and those with chronic infectious or malignant diseases (n = 4) were excluded. Patients were divided into three groups according to their antidiabetic therapy: group 1 consisted of patients on oral antidiabetic drug therapy (n = 12), group 2 of those on insulin therapy (n = 42), and group 3 of those being treated with diet alone (n = 10). At the start of HD and 12 months later, we measured fasting plasma glucose (FPG), HbA1c, the incidence of hypoglycemia (n/patient/ month), cholesterol, triglycerides, body weight, and insulin requirements in the insulin-treated groupC-peptide was only measured at the start of dialysis.

 We evaluated changes in antidiabetic therapy during the first year on dialysis, and the prevalence of vascular disease in each group at the start of HD.

Results

- FPG and HbA1c values were similar in all groups at the start of HD and after 1 year. Hypoglycemia occurred more frequently in insulin-treated patients; however, the difference was not significant. Cholesterol levels were similar in all groups, whereas triglycerides were significantly lower in insulin-treated patients (138 ± 28 vs. 176 ± 46 mg/dl; P\0.05). Body weight was similar in all groups. No significant change in body weight was observed in any group after 12 months on dialysis. At the start of HD, C-peptide levels were lower in insulin-treated patients than in the other groups (1.8 ± 0.9 ng/ml vs. 2.2 ± 1.1 and 2.4 ± 1.1 ng/ml; P\0.05). During the first 12 months on HD, two patients from group 1 were shifted to group 3 (diet alone), while four patients could reduce their drug dosage (33%). However, two subjects became insulin-dependent. In group 2, insulin therapy could be terminated in two cases, while the insulin dose could be reduced in 20 patients (48%). In group 3, one patient was switched to oral antidiabetic therapy. The prevalence of vascular disease was slightly higher in group 3 (NS).

Conclusion

- Within 1 year after the start of HD, the dose of sulfonylurea as well as insulin could be reduced in a large majority of patients.

- Metabolic control was similar in all groups. Only triglycerides were significantly lower in group 2.

- The frequency of hypoglycemia and the prevalence of vascular disease were just slightly higher in the group on insulin therapy

- In diabetic hemodialysis patients, poor glycemic control is a significant, independent predictor of the emergence of CVD, indicating the importance of careful management of glycemic control in hemodialysis patients.

Thank you

M.Sobh

Options for Antidiabetic Treatment

Insulin Resistance

Metformin

Pioglitazone

Rosiglitazone

Insulin Secretion

Glucose independent

Sulfonylurea

Glinides

Exogenous Insulin

Glucose dependent

DPP-4 Inhibitors
(Sitagliptin, Vildagliptin)

GLP-1 Mimetics
(Exenatide, Liraglutide)

Inhibition of Glucose Resorption

α-Glucosidase Inhibitors
(Acarbose, Miglitol, Voglibose)

Incretin-Based Therapies: Cardiovascular Risk Factors

- **Studies suggest GLP-1 mediated therapies may have beneficial effects on cardiovascular risk factors**
    - Body weight
    - Blood pressure
    - Lipids
    - Oxidative stress markers

Therapy	Events Included in Analysis*	RR, IR, or HR†	95% CI of ratio
Exenatide	CVD-extended events	0.69 RR	0.46 to 1.04
Liraglutide	MACE	0.73 IR	0.38 to 1.41
Sitagliptin	MACE	0.68 RR	0.41 to 1.12
Saxagliptin	CVD event	0.43 RR	0.22 to 0.86
Linagliptin	CVD composite	0.34 HR	0.16 to 0.70

*CVD-extended events = myocardial infarction/ischemia, stroke, cardiac death, arrhythmia, revasc. procedures, heart failure; MACE = major adverse cardiovascular events, CVD event = myocardial infarction, ischemic stroke, revasc. procedure; CVD composite = CV death, nonfatal stroke/myocardial infarction, hospitalization for unstable angina pectoris

†RR = relative risk, IR = incidence ratio, HR = hazard ratio

Fineman MS, et al. *Diabetes Obes Metab.* 2012.

Sulfonylureas and Meglitinides: Summary and Conclusions

- **Sulfonylureas** and **meglitinides** become hazardous as GFR decreases due to hypoglycemia

- **Glipizide** is the preferred sulfonylurea in CKD, but fasting glucose monitoring may be merited

- **Meglitinides**, particularly **repaglinide**, may have some advantage versus sulfonylureas in terms of hypoglycemic events

Metformin

- Metformin is eliminated unchanged in the urine

- FDA: Contraindicated in renal dysfunction
  (SCr ≥1.5 mg/dL in men; 1.4 mg/dL in women)
  - Secondary to fear of lactic acidosis
  - Up to 50% mortality in metformin-induced lactic acidosis

- NICE recommends the following:
  - Use with caution if eGFR <45 mL/min/1.73 m^2
  - Discontinue if eGFR <30 mL/min/1.73 m^2

Sirtori CR and Pasik C. *Pharmacol Res.* 1994; Hamilton CA. *J Ren Care.* 2012; Vasisht KP, et al. *Diabetes Obes Metab.* 2010.

Bile Sequestrant: Colesevelam

- Demonstrated to lower A1C by 0.5% versus placebo

- Therapy not generally associated with weight gain or hypoglycemia

- Minimally absorbed from GI tract, and therefore has no renal dosing adjustments

- Reasonable adjunctive therapy in patients with CKD and hypercholesterolemia

FDA Prescribing Instructions; Fonseca VA, et al. *Diabetes Obes Metab*. 2010.

Ergoline: Quick-Release Bromocriptine

- Bromocriptine's mechanism of action in diabetes is unknown
  - May alter circadian neuroendocrine rhythms
- Associated with a A1C decline of 0.4-0.6%
- Only quick-release bromocriptine is approved for the treatment of diabetes
- Bromocriptine has kinetics favorable in CKD
  - 5% renal elimination
  - 85% fecal elimination
  - Not generally associated with hypoglycemia

FDA Prescribing Instructions; Scranton RE, et al. *BMC Endocr Disord*. 2007.

α-Glucosidase Inhibitors: Acarbose and Miglitol

- **Acarbose** has a bioavailability of 34% and its metabolites are renally eliminated
  - In patients with CrCl <25 mL/min, acarbose AUC is increased by 5-6x
  - Case reports of hepatotoxicity
  - Unclear if renal failure affects risk

- **Miglitol** has a variable bioavailability and is exclusively (~96%) renally eliminated
  - Half-life increases significantly with declining GFR
  - Consequences unknown
  - Not studied in renal impairment

- Both accumulate in renal impairment and are contraindicated
  - FDA: Not recommended in patients with an SCr ≥2 mg/dL

FDA Prescribing Instructions; Salvatore T and Giugliano D. *Clin Pharmacokinet.* 1996; Scott LJ and Spencer CM. *Drugs.* 2000.
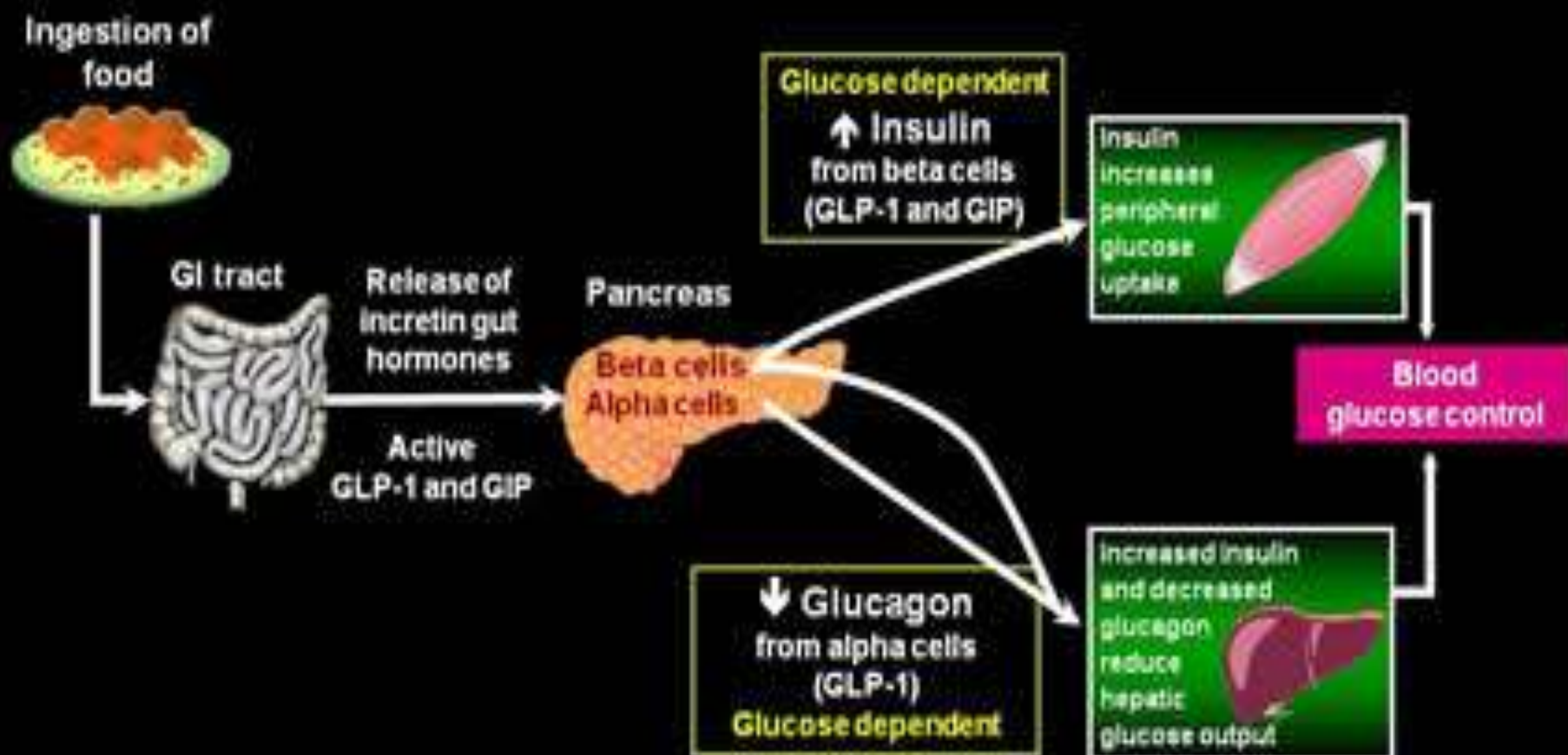
Thiazolidinediones

- Thiazolidinediones have multiple concerns not unique to CKD
    - Heart failure, fractures, bladder CA
- The risk of heart failure is further increased with:
    - CKD
    - Insulin use
    - Previous MI
- Fracture risk may be of concern in CKD, in setting of renal bone disease
    - TZDs have been demonstrated to increase urinary calcium excretion

Incretin-based therapy of Type 2DM : Incertin Mimetics Vs. Incertin Enhancers
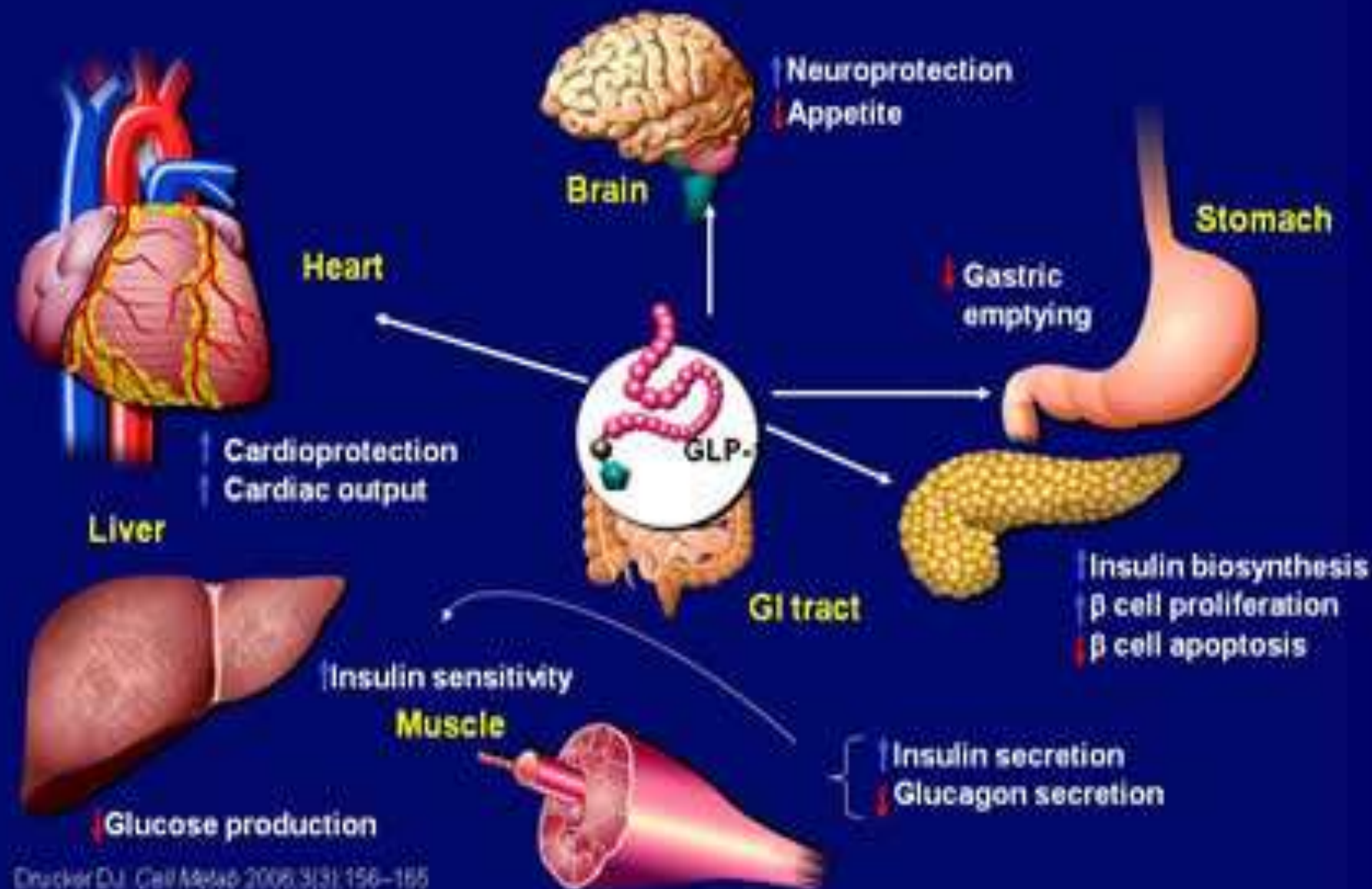
Mimetics (Exenatide, Liraglutide):

- High plasma concentrations of GLP-1-Ractivator
- Strong effects on all receptors: appetite↓ .Food intake↓ body water ↓,beta cells↑,alpha cells↓ cardiovascular effects?
- Tendency to cause GL side effects (Nausea)
- Injectables(so far), once or twice daily ,later once per week .
- HbA1c loweing :about 1%

Enhancers (Sitagliptin, vildagliptin , Alogliptin):

- Orally activate, once or twice daily
- Very few side effects
- Modest elevations of incertin hormone concentrations.
- Weight neutral and no GL side effects
- HbA1c loweing :about 0.7-0.8%

Summary of Incretin Actions on Different Target Tissues

Brain
- Neuroprotection
- Appetite

Heart

Stomach
- Gastric emptying

Liver
- Cardioprotection
- Cardiac output

GLP-

GI tract

Pancreas
- Insulin biosynthesis
- β cell proliferation
- β cell apoptosis

- Insulin sensitivity

Muscle

- Insulin secretion
- Glucagon secretion

- Glucose production

Drucker DJ. Cell Metab 2006;3(3):156–165

Effect of Renal Insufficiency on the pharmacokinetics or sitagliptin, a Dipeptidyl peptidase-4 inhibitor

Bergman AJ et al, Diabetes Care 2007 ;30:1862

- Renal excretion is the primary mechanism of elimination for sitagliptin.
- Adjustments for dosage of sitagliptin are needed according to renal function .

  ➢ No adjustment for patients with mild RI (Cr Cl 50-80ml/min).

  ➢ A twofolod decrease of the clinical dose of 100 mg q .d. (i.e,50 mg.q.d.)in moderate Rl(Cr Cl 30-50 ml/min)

  ➢ A fourfold decrease in the clinical dose (25 mg q .d.) in sever Rl (CR Cl30 ml/min)or ESRD

  Rl:Renal insufficiency

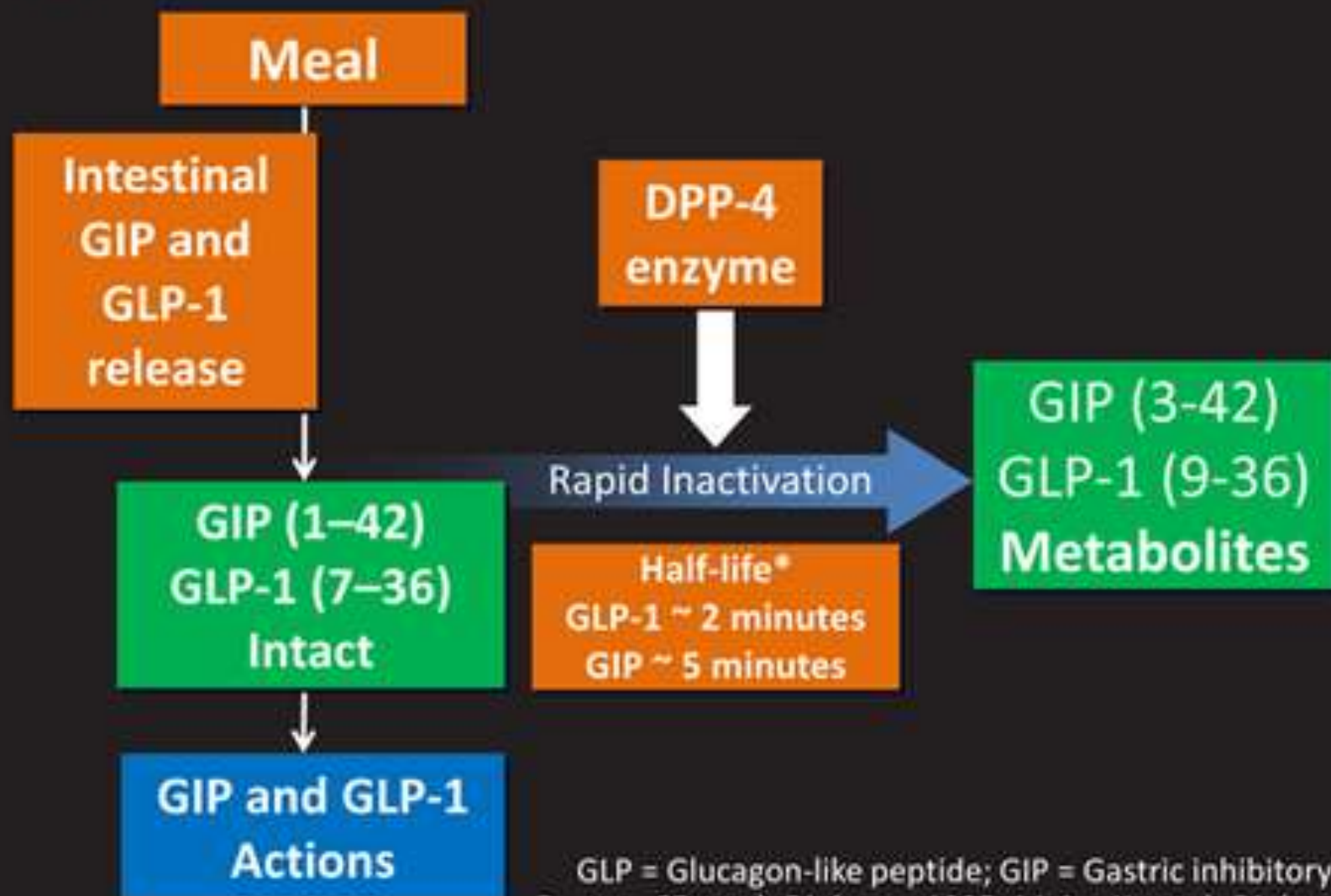# Effect of Renal Impairment on the Pharmacokinetics of Exenatide

- Evaluation of the pharmacokinetics, safety and tolerability of a single exenatide dose in patients with Renal Impairment (RI)

- Exenatide (5 or 10 mg) was injected subcutaneously in 31 subjects stratified by renal function:

  - ▶ normal (>80 ml/min)
  - ▶ mild RI (51–80 ml/min)
  - ▶ moderate RI (31–50 ml/min)
  - ▶ End-stage renal disease (ESRD) requiring haemodialysis

- Mean half-life of Exenatide for healthy, mild RI, moderate RI and ESRD groups were 1.5, 2.1, 3.2 and 6.0 h, respectively.

Effect of Renal Impairment on the pharmacokinetics of Exenatide

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GLP-1 and GIP: Degradation by DPP-4

Meal

Intestinal GIP and GLP-1 release

DPP-4 enzyme

GIP (1–42) GLP-1 (7–36) Intact

Rapid Inactivation

Half-life*
GLP-1 ~ 2 minutes
GIP ~ 5 minutes

GIP (3-42)
GLP-1 (9-36)
Metabolites

GIP and GLP-1 Actions

GLP = Glucagon-like peptide; GIP = Gastric inhibitory peptide
Deacon CF, et al. *Diabetes*. 1995; Meier JJ, et al. *Diabetes*. 2004.

Exenatide *Immediate-Release* Injection

- Predominantly eliminated by glomerular filtration
- May be used without dose adjustment if CrCl >50 mL/min
- Dose should be escalated from 5-10 mcg with caution if CrCl=30-50 mL/min
- Renal impairment may increase the risk of hypoglycemic episodes, especially if also using a sulfonylurea
- Renal impairment has occurred in patients with h/o N/V/D, with or without dehydration

> FDA: "Exenatide should not be used in patients with severe renal impairment (<30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. Caution should be applied when initiating exenatide or escalating the dose in patients with moderate renal failure."

FDA Prescribing Instructions; Hamilton CA. *J Ren Care*. 2012.

Exenatide *Extended-Release* Injection

- Predominantly eliminated by glomerular filtration

- May be used without dose adjustment if CrCl >50 mL/min

- Renal dysfunction may increase the risk of hypoglycemic episodes, especially if also using SU

- Renal impairment has occurred in patients with h/o N/V/D, with or without dehydration

FDA: "Exenatide ER should not be used in patients with severe renal impairment (CrCl<30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of 5 mcg were not well tolerated due to GI side effects. Caution should be applied when initiating exenatide ER in patients with moderate renal impairment (CrCl=30-50 mL/min)."

FDA Prescribing Instructions; Hamilton CA. *J Ren Care.* 2012.

Liraglutide

- Cautioned for use in patients with CrCl <60 mL/min

- A 2011 meta-analysis found:
  - No differences in efficacy or ADRs with mild renal impairment
  - Reduction of cardiovascular risk factors (body weight, systolic blood pressure) in mild renal impairment
  - Severe renal impairment (CrCl <30 mL/min) was associated with increased nausea and hypoglycemia rates, but sustained effectiveness

> FDA: "There is limited experience in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Liraglutide should be used with caution in this patient population. No dose adjustment is recommended for patients with renal impairment."

FDA Prescribing Instructions; Davidson JA, et al. *Endocr Pract*. 2011.

GLP-1 Receptor Agonists: Summary and Conclusions

- GLP-1 receptor agonists have a variable effect:
  - Exenatide IR and exenatide ER should not be used in patients with CrCl <30 mL/min
  - The dose of exenatide IR must be escalated with caution when CrCl is 30-50 mL/min
  - Liraglutide should be used with caution in CKD, and ADRs must be considered

- As a class, DPP-4 inhibitors are relatively safe and have few drug interactions

- Rising serum drug levels of DPP-4 inhibitors may be problematic as GFR declines

- Linagliptin, however, is primarily eliminated fecally and can safely be used without regard to renal function